

AMENDMENTS TO THE CLAIMS

In the Claims:

Please amend claims 1, 3, 7, 9, 23-26, 29, 42, and 43 and add new claims 47-82, as shown in the following listing of claims, which will replace all prior versions and listings of claims in the application. Applicants hereby withdraw non-elected claims 10-21 and 31-41 and cancel claims 2, 4-6, and 27, both without prejudice to the pursuit of these claims in an appropriate divisional or continuation application.

Listing of claims:

1 (currently amended). A method for inducing formation of new lymphatic vessels in a mammal, wherein the method comprises administering to the mammal an effective amount of vascular endothelial growth factor (VEGF) factor 2 (VEGF-2) or an effective fragment thereof sufficient to form the new vessels in the mammal; and repeating the administration at least twice, wherein the VEGF-2 or VEGF-2 fragment is sufficient to decrease ear volume by at least about 10% as determined by a standard rabbit ear assay and the VEGF-2 or VEGF-2 fragment exhibits at least about 70% of the lymph vessel promoting activity of the VEGF-2 in the assay.

2 (canceled).

3 (currently amended). The method of claim 1, wherein the amount of the ~~VEGF~~ VEGF-2 administered to the mammal is sufficient to increase the number of lymphatic vessels by at least about 10% as determined by a standard lymphoscintigraphy assay.

4. – 6. (canceled)

7 (currently amended). The method of claim 1, wherein the ~~mammal has, is suspected of having, or will have~~ lymphedema or ~~[[a]]~~ medical condition associated with same ~~such as comprises~~ lymphangietasia, lymphangioma, ~~and/or~~ lymphangiosarcoma.

8 (original). The method of claim 7, wherein the lymphedema is primary or secondary lymphedema.

9 (currently amended). The method of claim 1, wherein the ~~VEGF~~VEGF-2 is co-administered with at least one angiogenic protein.

10 (withdrawn). A method for preventing or reducing the severity of lymphatic vessel damage in a mammal, wherein the method comprises administering to the mammal an effective amount of vascular endothelial growth factor (VEGF); and exposing the mammal to conditions conducive to damaging the lymphatic vessels, the amount of VEGF being sufficient to prevent or reduce the severity of the vessel damage in the mammal.

11 (withdrawn). The method of claim 10, wherein the conditions conducive to the lymphatic vessel damage are an invasive manipulation, disease, genetic predisposition, congenital (onset less than about two years after birth), lymphedema precox, lymphedema tarda, or trauma.

12 (withdrawn). The method of claim 11, wherein the invasive manipulation is surgery such as ilio-femoral bypass, regional lymph node dissection including axillary (post-mastectomy lymphedema), pelvic and para-aortic (leg and groin lymphedema), and neck (head and neck lymphedema).

13 (withdrawn). The method of claim 11, wherein the disease is a neoplastic disease, rheumatoid arthritis, filariasis or recurrent infection such as erysipelas.

14 (withdrawn). The method of claim 13, wherein the neoplastic disease is hodgkin lymphoma, metastatic cancer, or a cancer of the prostate or breast, cervical cancer or melanoma.

15 (withdrawn). The method of claim 11, wherein the trauma is associated with a medial aspect of a thigh.

16 (withdrawn). The method of claim 11, wherein the genetic predisposition is familial autosomal dominant.

17 (withdrawn). The method of claim 16, wherein the predisposition is Nonne-Milroy disease.

18 (withdrawn). The method of claim 11, wherein the genetic predisposition is familial and non-dominant.

19 (withdrawn). The method of claim 11, wherein the congenial lymphatic vessel damage is sporadic.

20 (withdrawn). The method of claim 11, wherein the lymphedema precox (onset between about 2 and 35 years of age) is familial, autosomal recessive such as Meige disease.

21 (withdrawn). The method of claim 11, wherein the lymphedema precox is sporadic.

22 (original). The method of claim 8, wherein the primary lymphedema is associated with one or more of a distal obliteration, proximal obliteration, or hyperplasia.

23 (currently amended). The method of claim 7, wherein the ~~VEGF~~VEGF-2 is administered to the mammal at least about 12 hours before exposing the mammal to the conditions conducive to damaging the lymphatic vessels.

24 (currently amended). The method of claim 23, wherein the ~~VEGF~~VEGF-2 is administered to the mammal between from about 1 to 10 days before exposing the mammal to the conditions conducive to damaging the vessels.

25 (currently amended). The method of claim 22, wherein the method further comprises administering the ~~VEGF~~VEGF-2 to the mammal following the exposure to the conditions conducive to damaging the vessels.

26 (currently amended). A method for treating lymphedema in a mammal in need of such treatment, wherein the method comprises administering to the mammal an effective amount of vascular endothelial growth ~~factor~~factor 2 (VEGF-2) or an effective fragment thereof sufficient to form the new vessels in the mammal; and repeating the administration at least twice, wherein the VEGF-2 or VEGF-2 fragment is sufficient to decrease ear volume by at least about 10% as determined by a standard rabbit ear assay and the VEGF-2 or VEGF-2 fragment exhibits at least about 70% of the lymph vessel promoting activity of the VEGF-2 in the assay.

27. (canceled)

28 (previously presented). The method of claim 25 further comprising co-administering at least one angiogenic protein.

29 (currently amended). The ~~methods~~method of claim 1, wherein the mammal is a rabbit, a rodent or a primate.

30 (original). The method of claim 29, wherein the primate is a human patient.

31 (withdrawn). A pharmaceutical product for inducing growth of new lymphatic vessels in a mammal, wherein the product comprises vascular endothelial factor 2 (VEGF-2) or an effective fragment thereof.

32 (withdrawn). The pharmaceutical product of claim 31 in which the VEGF-2 is formulated to be physiologically acceptable to a mammal.

33 (withdrawn). The pharmaceutical product of claim 32, wherein the product is sterile and comprises VEGF-2 protein or nucleic acid encoding the protein.

34 (withdrawn). A kit for the treating lymphedema in a human patient, wherein the kit comprises VEGF-2 protein, nucleic acid encoding VEGF, or an effective fragment thereof; the kit optionally further comprising a pharmacologically acceptable carrier solution, means for delivering the VEGF-2 protein or nucleic acid and directions for using the kit.

35 (withdrawn). The kit of claim 34, wherein the means for delivering the VEGF-2 protein or nucleic acid is a stent, catheter or syringe.

36 (withdrawn). A test system for identifying compounds that reduce lymphedema, the system comprising:

- a) a mammal characterized by having a surgically manipulated appendage, the manipulation being sufficient to expose a neurovascular bundle (NVB) in the ear and to provide a substrate for detecting neolymphatic growth,
- b) a candidate compound for reducing lymphedema in the mammal; and

c) at least one implementation for detecting an increase or decrease in appendage thickness following contact of the candidate compound with the NVB.

37 (withdrawn). The test system of claim 36, wherein the mammal is a rabbit.

38 (withdrawn). The test system of claims 36-37, wherein the candidate compound comprises vascular endothelial factor (VEGF); or an effective fragment thereof.

39 (withdrawn). The test system of claim 38, wherein the VEGF is VEGF-2 or an effective fragment thereof.

40 (withdrawn). The rabbit VEGFR-3 cDNA sequence shown in Figure 21.

41 (withdrawn). The rabbit VEGFR-3 amino acid sequence shown in Figure 22A.

42 (currently amended). The method of claim 4, wherein the amount of the ~~VEGF~~VEGF-2 administered to the mammal is sufficient to increase growth of new lymphatic vessels following lymphedema.

43 (currently amended). The method of claim 4, wherein the ~~VEGF~~VEGF-2 is co-administered with at least one angiogenic agent.

44 (previously presented). The method of claim 26 further comprising co-administering at least one angiogenic protein.

45 (previously presented). The method of claim 26, wherein the mammal is a rabbit, a rodent or a primate.

46 (previously presented). The method of claim 45, wherein the primate is a human patient.

47 (new). The method of claim 1, wherein the administration is repeated over a period of about two weeks.

48 (new). The method of claim 26, wherein the administration is repeated over a period of about two weeks.

49 (new). The method of claim 26, wherein the amount of the VEGF-2 administered to the mammal is sufficient to increase the number of lymphatic vessels by at least about 10% as determined by a standard lymphoscintigraphy assay.

50 (new). The method of claim 26, wherein the amount of the VEGF-2 administered to the mammal is sufficient to increase growth of new lymphatic vessels following lymphedema.

51 (new). The method of claim 50, wherein the increase in new lymphatic vessel grow is at least about 10% as determined by standard lymphoscintigraphy.

52 (new). The method of claim 26, wherein the lymphedema or medical condition associated with same comprises lymphangietasia, lymphangioma, or lymphangiosarcoma.

53 (new). The method of claim 52, wherein the lymphedema is primary or secondary lymphedema.

54 (new). The method of claim 53, wherein the primary lymphedema is associated with one or more of a distal obliteration, proximal obliteration, or hyperplasia.

55 (new). The method of claim 26, wherein the mammal is a rabbit, a rodent or a primate.

56 (new). The method of claim 55, wherein the primate is a human patient.

57 (new). A method for inducing formation of new lymphatic vessels in a mammal, wherein the method comprises administration to a mammal of an effective amount of vascular endothelial growth factor 2 (VEGF-2) or an effective fragment thereof sufficient to form the new vessels in the mammal, wherein the administration comprises injection into cells or tissues of the mammal.

58 (new). The method of claim 57, wherein:

- a. the mammal is at risk for, is suspected of being at risk for, or will have lymphedema or a medical condition associated with same; and
- b. the VEGF-2 is administered to the mammal before exposing the mammal to conditions conducive to damaging lymphatic vessels.

59 (new). The method of claim 57, wherein the administration further comprises co-administering at least one angiogenic protein.

60 (new). The method of claim 57, wherein the administration is through a stent, a catheter, or a syringe.

61 (new). The method of claim 57, wherein the mammal comprises a rabbit, a rodent, or a primate.

62 (new). A method for inducing formation of new lymphatic vessels in a mammal, wherein the method comprises administration to a mammal of an effective amount of vascular endothelial growth factor 2 (VEGF-2) or an effective fragment thereof sufficient to form the new vessels in the mammal, wherein the administration comprises topical application.

63 (new). The method of claim 62, further comprising:

- a. exposure of a tissue surface of the mammal; and
- b. topical application of the effective amount of VEGF-2 or an effective fragment thereof.

64 (new). The method of claim 62, wherein:

- a. the mammal is at risk for, is suspected of being at risk for, or will have lymphedema or a medical condition associated with same; and
- b. the VEGF-2 is administered to the mammal before exposing the mammal to conditions conducive to damaging lymphatic vessels.

65 (new). The method of claim 62, wherein the administration further comprises co-administering at least one angiogenic protein.

66 (new). The method of claim 62, wherein the topical application comprises administration of a gel or gelling agent comprising the effective amount of VEGF-2 or an effective fragment thereof.

67 (new). The method of claim 66, wherein the gel or gelling agent comprises a polysaccharide.

68 (new). The method of claim 67, wherein the gel or gelling agent is between 1% and 90% w/w polysaccharide.

69 (new). The method of claim 68, wherein the gel or gelling agent is between 1% and 20% w/w polysaccharide.

70 (new). The method of claim 67, wherein the polysaccharide comprises a water-soluble polysaccharide.

71 (new). The method of claim 70, wherein the water-soluble polysaccharide comprises hyaluronic acid, a starch or a cellulose derivative.

72 (new). The method of claim 71, wherein the cellulose derivative comprises methylcellulose, hydroxyethylcellulose, or carboxymethylcellulose.

73 (new). The method of claim 62, wherein the mammal comprises a rabbit, a rodent, or a primate.

74 (new). A method for inducing formation of new lymphatic vessels in a mammal, wherein the method comprises administration to a mammal of an effective amount of vascular endothelial growth factor 2 (VEGF-2) or an effective fragment thereof sufficient to form the new

vessels in the mammal, wherein the administration comprises introduction of a nucleic acid encoding VEGF-2 or an effective fragment thereof into the mammal resulting in the uptake and expression of the nucleic acid by the cells.

75 (new). The method of claim 74, wherein:

- a. the mammal is at risk for, is suspected of being at risk for, or will have lymphedema or a medical condition associated with same; and
- b. the VEGF-2 is administered to the mammal before exposing the mammal to conditions conducive to damaging lymphatic vessels.

76 (new). The method of claim 74, wherein the administration further comprises co-administering at least one angiogenic protein.

77 (new). The method of claim 74, wherein the nucleic acid comprises a vector.

78 (new). The method of claim 77, wherein the vector comprises a DNA viral vector.

79 (new). The method of claim 74, wherein the method further comprises infection, transfection, transduction, or transformation.

80 (new). The method of claim 74, wherein the mammal comprises a rabbit, a rodent, or a primate.

81 (new). A method for inducing formation of new lymphatic vessels in a mammal, wherein the method comprises administering to the mammal an effective amount of vascular endothelial growth factor 2 (VEGF-2) or an effective fragment thereof sufficient to form the new vessels in the mammal, wherein:

- a. the mammal has, is suspected of having, or will have lymphedema or a medical condition associated with same; and
- b. co-administering at least one angiogenic protein.

82 (new). A method for inducing formation of new lymphatic vessels in a mammal, wherein the method comprises administering to the mammal an effective amount of vascular endothelial growth factor 2 (VEGF-2) or an effective fragment thereof sufficient to form the new vessels in the mammal, wherein:

- a. the mammal is at risk for, is suspected of being at risk for, or will have lymphedema or a medical condition associated with same; and
- b. the VEGF-2 is administered to the mammal before exposing the mammal to conditions conducive to damaging lymphatic vessels.